

EFFECT OF POTASSIUM PERCHLORATE ON THE FOETAL RABBIT THYROID

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The effect of protracted potassium perchlorate treatment from the beginning of pregnancy on the maternal and foetal thyroid glands has been studied in rabbits. The substance has been found to cause excessive hyperplasia and hyperfunction in the maternal and foetal gland alike. The increase in the relative weight of the foetal glands was more intensive than that of the maternal gland, a finding which is a sign of higher goitrogenic risks to the foetus and suggests that the foetal hypophyseothyroid system has functions of its own, independent from those of the maternal organism. Attention is drawn to the foetal risks involved by the treatment in question.

The adverse effects of intrauterine thyroid injury on physical and mental development have been widely discussed (BONGIOVANNI et al. [1956], FRENCH and VAN WYK [1964], HOOFT et al. [1962], JOB [1963], NEIMANN et al. [1963]). Iatrogenic factors account for a large number of such injuries. Potassium perchlorate treatment, claimed by its initiators (GODLEY and STANBURY [1954]) to be entirely harmless has been subsequently incriminated by others (GJEMDAL [1963], KRAATZ and MÄRZ [1960], KREVANS et al. [1962], SUNAR [1963], etc.) for goitrogenic and other effects. The increasing use of potassium perchlorate in the treatment of hyperthyroidism in recent years warrants investigations into its effects during pregnancy.

In earlier investigations we have found that thyroid ^{131}I uptake which is the first sign of the gland's activity (MITSKEVITCH and MAMULY [1953]) starts on the 20th day of foetal life in the rabbit (LAMPÉ et al. [1966a]). This is the stage when differentiation of the acini begins and the first traces of colloid appear. By the end of intrauterine life the microscopic or functional differences between the foetal and the maternal gland have disappeared, as reflected by identical histochemical reactions of both tissues (LAMPÉ et al. [1966b]).

Our investigations into the effect on the foetal thyroid of potassium perchlorate administered over the whole pregnancy were concerned with the following issues.

1. Do thyrostatic agents entering the foetal organism by the placental route, induce similar changes in the foetal as in the maternal gland?
2. Do these agents interfere with the normal differentiation of the thyroid gland?

Material and method

12 pregnant rabbits kept under identical nutritional and environmental conditions were given potassium perchlorate in doses of 100 mg/kg daily, mixed to a small portion of food, from the very start of pregnancy. Six animals were worked up on the 21st day, six others on the 28th day of pregnancy, our earlier experiments having shown differentiation of the thyroid gland to start on the 20th and to complete its course by the 28th day of pregnancy. We examined the maternal thyroids in order to check the effect of the drug. As a control, data for untreated rabbit foetuses obtained in earlier experiments were used.

At the end of the respective periods the animals were killed, the foetal thyroids removed and worked up, together with the maternal thyroid and pituitary glands for histological and histochemical study and statistical evaluation. The glands were freed from the adjacent tissues as completely as possible, then weighed and related to 100 g body weight. For staining, combined galloxyanin-orcein-eosin-methanyl-yellow and the haematoxylin chromatrope 2R method were used, and as histochemical methods, the PAS-reaction for the demonstration of glycoproteins (neutral mucopolysaccharides); toluidine blue, celestine blue and Hale's reaction for the demonstration of basophilic elements; tetrazotised benzidine for the demonstration of protein; diazonium for the demonstration of SS + SH groups.

The reason for selecting the foregoing reactions was to have found in earlier studies, in accordance with KROMPECHER et al. (1961a, 1961b, 1962), MÜLLER (1962), KOBAYASHI et al. (1959) and WALLRAFF (1959) that the substance which gives the thyroid gland its histochemical character is a neutral glycoprotein, the carrier of the actual thyroid hormones. By identifying the carbohydrate and the protein components of this substance the reactions will consequently define the secretory state of the thyroid.

Statistical evaluation of the microscopic picture allowed a reliable estimation of thyroid function. Owing to the inhomogeneous structure of the thyroid gland, we found the quantitative procedure of ERÄNKÖ (1955) and PALKOVITS (1963) based on the measurement of the acinus-epithelium-stroma ratio, more suitable for this purpose than measurements of nucleic acid variations. The maternal and foetal thyroid glands of untreated animals belonging to the same stages of pregnancy were studied by the same method.

The conclusions drawn from the present experiments have been based on a comprehensive evaluation of the evidence derived from the microscopical, histochemical and statistical methods and of the thyroid weights.

Results

Fig. 1 shows the relative maternal and foetal thyroid weights. The thyroids of the untreated pregnant animals weighed between 5.0 and 11.4 mg/100 g [average, 8.1 mg/100 g] on the 21st day and between 7.7 and 13.3 mg/100 g [average, 10.45 mg/100 g] on the 28th day. The thyroids of the foetuses of the same animals weighed between 11.7 and 18.7 mg/100 g [average, 13.8 mg/100 g] on the 21st day, and between 11.3 and 13.9 mg/100 g [12.5 mg/100 g] on the 28th day.

Ingestion of perchlorate has been found to cause an increase in maternal as well as in foetal thyroid weight. On the 21st day of treatment the maternal thyroids weighed between 10.3 and 28.9 mg/100 g (average, 21.7 mg/100 g), and the foetal thyroids, between 42.3 and 56.2 mg/100 g (average, 49.5 mg/100 g). In other words, the maternal thyroid reached nearly threefold, and the foetal gland, nearly fourfold its initial weight. Continued intake of perchlorate further enhanced the increase in thyroid weight, particularly in the foetus. The maternal gland weighed between 28.3 and 51.1 mg/100 g (average, 41.0 mg/100 g), and the foetal gland, between 85.0 and 131.7 mg/100 g (average, 110.2 mg/100 g) on the 28th day.

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uptake. We have found in earlier studies, MÜLLER (1962), KOBAYASHI et al. the thyroid gland its histochemical thyroid hormones. By identifying the reactions will consequently

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have been based on a comprehensive, histochemical and statistical

thyroid weights. The thyroid weights between 5.0 and 11.4 mg/100 g between 7.7 and 13.3 mg/100 g thyroids of the foetuses of the 21st day [average, 13.8 mg/100 g] and 28th day [12.5 mg/100 g] on the

use an increase in maternal thyroid weight. After the treatment the maternal thyroid weight (average, 21.7 mg/100 g), and the foetal thyroid weight (average, 49.5 mg/100 g) increased nearly threefold, and the continued intake of perchlorate particularly in the foetus. The maternal thyroid weight (average, 41.0 mg/100 g) and the foetal thyroid weight (average, 131.7 mg/100 g) increased

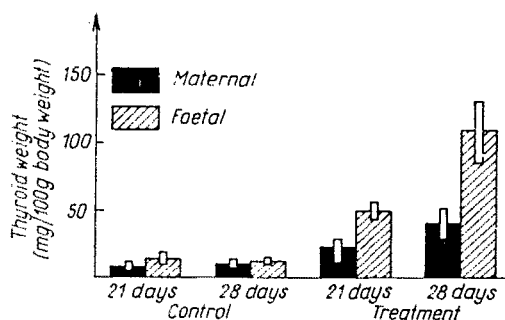


Fig. 1. Relative maternal and foetal thyroid weights in untreated rabbits and rabbits treated with potassium perchlorate, on the 21st and 28th days of pregnancy



Figs 2, 3, 4. Foetal rabbit thyroid on the 21st day of potassium perchlorate treatment continued from the beginning of pregnancy

Fig. 2. Glandular tissue consisting of dense trabeculae with minute acinar lumina. Gallo-cyanin-orcein-eosin-methanil-yellow staining (GOEM). Enlargement: $40 \times 1.5 \times 4.1$

Figs 3 and 4. Thyroid gland of the same rabbit foetus. PAS-reaction. The acini are lined with high cuboidal and columnar epithelial cells. The minute lumina contain PAS-positive colloid. Enlargement: as before

Microscopical changes produced by $KClO_4$ during the first 21 days of pregnancy

Foetal thyroid. The pattern is made up of dense trabeculae and occasional acini. The epithelial cells are cuboid in shape and contain round nuclei with a loose chromatin structure. The lumina of the scarce acini not wider than a pinhole contain PAS-positive colloid (Figs 2, 3, 4). Apart from higher epithelial cells neither the microscopical nor the histochemical picture differs from that seen in untreated animals. Statistical evaluation reveals a reduction in the relative number of the acini to 4 per cent as against 10 per cent in the controls, while the relative volume of the stroma has been found to increase from 39 per cent to 46 per cent. The proportion of the epithelium remained practically unchanged (Fig. 5).

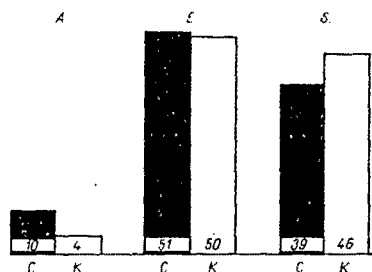


Fig. 5. Proportion of acini (A), epithelial cells (E) and stroma (S) in the foetal rabbit thyroid on the 21st day of potassium perchlorate treatment (K) and in untreated controls (C)

Maternal thyroid. The microscopic pattern is dominated by acini lined with a high columnar epithelium interspersed by cuboidal cells. The acini contain traces of PAS-positive colloid of a very loose, foamy structure. The apical zone of the columnar cells shows an excessive number of PAS-positive granules. The microscopic picture is thus characteristic of hyperfunction (Figs 6, 7). The distinctive change in relation to the maternal glands belonging to the same stage of pregnancy is hyperfunction. Statistical evaluation shows a reduction in the percentage of acini and a parallel increase in that of functioning epithelial cells with no quantitative change of the stroma (Fig. 8).

Ingestion of $KClO_4$ between the first and 28th day of pregnancy

Foetal thyroid. The greatly enlarged hyperplastic gland is made up of acini with a lining of columnar epithelium and very narrow, invariably colloid-free, lumina (Figs 9, 10). The absence of colloid deposits, the structural signs of epithelial hyperfunction and retarded development of the acini are in sharp contrast with the pattern found in the foetuses of untreated animals. Statistical evaluation shows a reduction in the relative number of acini and a parallel increase in that of the epithelial cells (Fig. 11).

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stroma (S) in the foetal rabbit thyroid (K) and in untreated controls (C)

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28th day of pregnancy

hyperplastic gland is made up of very narrow, invariably colloid-filled deposits, the structural signs of the acini are in sharp contrast with untreated animals. Statistical evaluation reveals a parallel



Figs 6 and 7. Thyroid gland of rabbit on the 21st day of pregnancy. Treatment with perchlorate from the first day of pregnancy

Fig. 6. Hyperfunctioning tissue. GOEM-staining. Enlargement: as on Fig. 2.

Fig. 7. PAS-positive colloid and granules in the apical zone of the epithelial cells. Enlargement: as above

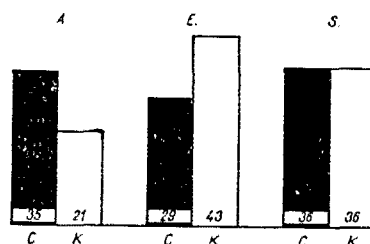
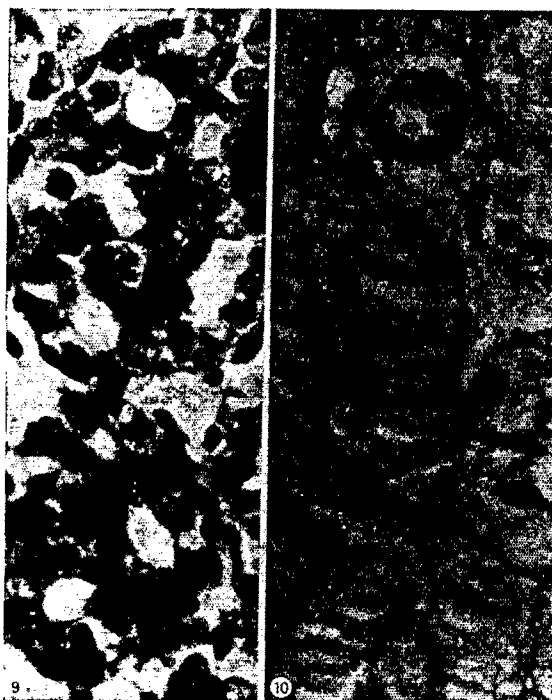


Fig. 8. A—E—S ratio in the maternal thyroid on the 21st day

Maternal thyroid. The acini are lined with columnar epithelium and contain PAS-positive, loose, sporadically dense, colloid (Figs 12, 13, 14, 15). The glandular hyperfunction is in sharp contrast with the glands of untreated animals being in the same stage of pregnancy. Statistical evaluation reveals



Figs 9 and 10. Foetal thyroid on the 28th day; potassium perchlorate having been administered since the first day of pregnancy

Fig. 9. Differentiation of acini and dense trabeculae. No colloid deposits. High cuboidal glandular epithelium. GOM-staining. Enlargement: as before

Fig. 10. PAS-reaction. The basement membrane and the apical membrane of the glandular epithelial cells are PAS positive. No colloid reaction. Enlargement: as before

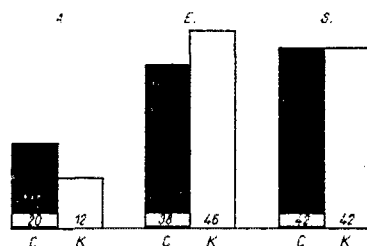


Fig. 11. Quantitative relation between A—E—S in the foetal gland on the 28th day

a reduction in the relative number of acini and an increased proportion of epithelial cells and stroma (Fig. 16).

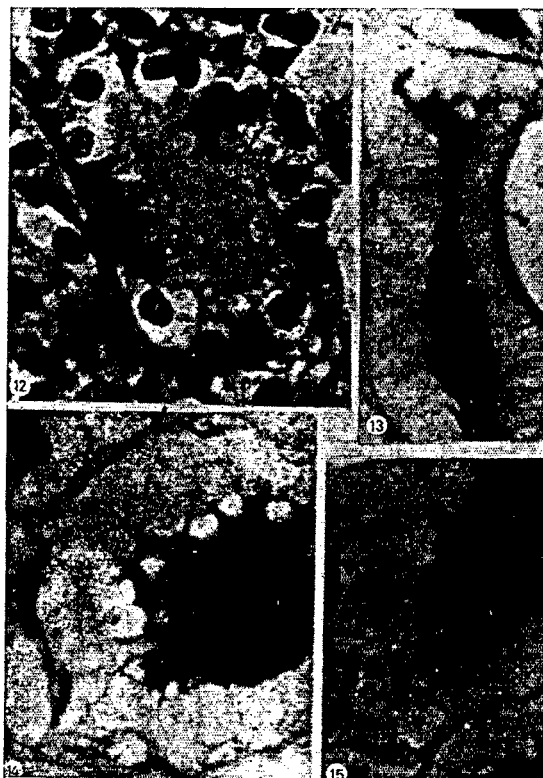
Maternal hypophysis. Among the beta cells many vacuolated, typically degranulated "thyroidectomy-cells" are seen regardless whether treatment has been of 21 or 28 days duration.

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Figs 12—15. Thyroid gland of rabbit on the 28th day of pregnancy. Treatment with potassium perchlorate from the first day of pregnancy.

Fig. 12. Excessive glandular hyperfunction. Acini lined with high columnar epithelium. Occasional round giant cells with loose clear plasma. GOEM-staining. Enlargement: as before

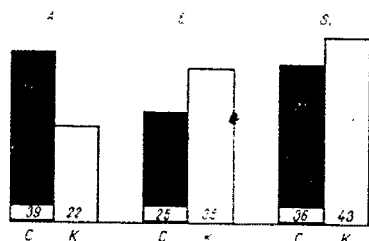


Fig. 16. Quantitative relation between A—E—S in the maternal thyroid on the 28th day

Discussion

The antithyroid activity of KClO_4 due to its thyroxine synthesis blocking effect has been shown by means of ^{131}I by WYNGAARDEN (1952) and confirmed morphologically by KRÜSKEMPER and KLEINSORG (1954).

The mechanism of iodine concentration by the thyroid, as the first step in the synthesis of thyroid hormone is claimed by LEWITUS et al. (1961), GRAB and OBERDISSE (1959) to be due to a binding of iodine by adsorption, a process in which the thyroid is supposed to play the role of a specific protein ion-exchanger. In opposition to this, HALMI et al. (1956, 1961) regard the accumulation of iodine as an energy-consuming active transfer process. Perchlorate inhibits the iodine-concentrating activity of the thyroid as well as in other systems in which iodine is deposited, i.e. in the salivary glands, in the gastric wall, etc. (WYNGAARDEN et al. [1953], HALMI et al. [1956], KUTZIM et al. [1963]). A comparative antagonism blocking the access of iodine to the thyroid is ascribed to KClO_4 by WYNGAARDEN, a claim consistent with the finding of ANBAR et al. (1959) that ^{36}Cl and ^{18}O labelled KClO_4 is stored in the thyroid. The fact that KRÜSKEMPER and REILICH (1959) have been able to neutralize the effect of KClO_4 by KJ administration also supports this theory.

In the light of the foregoing experimental evidence as well as of numerous clinical observations (LÓRINCZ and ANDOR [1956], SZÁNTÓ [1964]) the manner in which KClO_4 takes effect may be outlined as follows. The substance most certainly interferes with iodine uptake whether through a competitive antagonism or a blocking effect on the enzymes providing for the accumulation of iodine. The consequence is a reduced production of thyroid hormone and a fall of the blood hormone level. This in turn elicits an enhanced production of TSH. This results in enlargement and hyperplasia of the thyroid gland the extent of which is related to KClO_4 -intake. Involvement of the pituitary gland by the process has been demonstrated by EGER et al. (1955) by the finding of thyroidectomy-cells associated with low thyroxine levels.

As suggested by our findings, the permeability of the placental barrier to KClO_4 enables this substance to cause the same changes in the foetal thyroid as in the maternal gland, namely intensive hyperplasia as a sign of hyperfunction, and on the evidence of statistical calculations, a relative reduction in the number of acini with an increase in epithelial elements and stroma, associated with a loss or complete disappearance of colloid. In untreated animals, the relative weights of maternal and foetal glands have been found practically identical at the given stages of pregnancy, whereas under the effect of KClO_4 , a significant enlargement of the foetal thyroid is demonstrable on the 21st, still more so on the 28th day of pregnancy. This finding conclusively shows, in agreement with the results of NIKITOVITCH and KNOBIL (1955) and of POSTEL (1957) that the pituitary-thyroid system of the foetus functions independently of its maternal counterpart, otherwise enlargement of the maternal thyroid would be, obviously, more intense than that of the foetal gland. Increased sensitivity of the foetal thyroid may be due either to a deficient function of the enzymes responsible for iodine uptake or to an undue accumulation of perchlorate. Both possibilities require further study.

the thyroid, as the first step by LEWITUS et al. (1961), of iodine by adsorption, the role of a specific protein (1956, 1961) regard the active transfer process. Perchlorate of the thyroid as well as in the salivary glands, in the LMI et al. [1956], KUTZIM the access of iodine to the thyroid claim consistent with the claim that labelled $KClO_4$ is stored in the thyroid (1959) have been able to also supports this theory. Evidence as well as of numerous (SZÁNTÓ [1964]) the manner follows. The substance most through a competitive antagonism for the accumulation of thyroid hormone and a fall in enhanced production of iodine of the thyroid gland the function of the pituitary gland (1955) by the finding of iodine levels.

of the placental barrier to changes in the foetal thyroid function as a sign of hyperfunction—a relative reduction in the contents and stroma, associated with. In untreated animals, the changes have been found practically under the effect of $KClO_4$, demonstrable on the 21st day, which conclusively shows, in agreement with OBIL (1955) and of POSTEL (1955) functions independently of the maternal thyroid function of the foetal gland. Increased iodine to a deficient function of the thyroid and undue accumulation of iodine.

In evaluating our results, allowance must be made for the fact that the animals used in the study were healthy and euthyroid. In clinical practice, however, the reason for prescribing $KClO_4$ during pregnancy is usually maternal hyperthyroidism in which case abnormal function of the foetal thyroid is exceptional. Consequently, $KClO_4$, while normalizing the function of the hyperthyroid maternal gland, unduly depresses the activity of the euthyroid gland of the foetus.

It must, therefore, be kept in mind that potassium perchlorate intake during pregnancy causes similar structural changes in the maternal and foetal thyroid and carries more severe goitrogenic risks to the foetus.

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